REMARKS

Upon entry of the amendments to the claims herein, claims 3 and 7-12 are pending. Claim 3 is amended; claims 1, 2, and 4-6 are withdrawn; and claims 7-12 are new. Support for the amendments to claim 3 can be found in the specification at page 4, lines 6-7 and at page 6, lines 22-28. Support for new claims 7 and 8 can be found at least at page 6, lines 12-16, and line 29. Support for new claim 9 can be found at least at page 5, lines 6-7. Support for new claims 10 and 11 can be found at least at page 5, lines 7-9 and at page 7, lines 1-2. Support for new claim 12 can be found at least at page 7, lines 1-3. No new matter has been added.

Objections to the Specification

The Examiner has objected to the specification. According to the Examiner, it is unclear whether some of the Examples are prophetic or have actually been carried out on a human patient because the tense of the verbs changes from past to present tense. Accordingly, Applicants have amended the specification at Examples to change the tense of the verbs to present tense where the Example is prophetic, and to past tense where the Example has actually been performed, as requested by the Examiner. This objection has been overcome and should be withdrawn.

Claim Objections

The Examiner objects to the use of the term "blood-substitute" in claim 3. According to the Examiner, the specification defines a "blood substitute" as a substitute which contains hemoglobin. Accordingly, Applicants have amended claim 3 to recite "a hemoglobin-containing" blood substitute, as requested by the Examiner. This objection has been overcome and should be withdrawn.

Claim Rejections under 35 U.S.C. § 112

35 U.S.C § 112, second paragraph

Claim 3 is rejected under 35 U.S.C § 112, second paragraph, as being indefinite. According to the Examiner, the metes and bounds of term "co-infusing" are uncertain because the length of time which co-infusing could be interpreted to be separately at a different time is not definite, and it is uncertain whether the term encompasses a mixing of the blood substitute

and inorganic nitrite in one container, then infused, or if they must be in separate containers. Applicants traverse with respect to claim 3 as amended herein.

Amended claim 3 recites a method of blood product transfusion comprising the steps of co-administering a hemoglobin-containing blood substitute and an inorganic nitrite into a patient via infusion, wherein the inorganic nitrite is infused at a rate of 0.01 to 10 micromoles per minute, and the hemoglobin-containing blood substitute is infused at a rate of 1 to 1000 cubic centimeters per hour. As amended, claim 3 requires the co-administration of the blood substitute and hemoglobin via infusion at different rates. As such, it is clear that the blood substitute and inorganic nitrite are administered at the same time but separately (*i.e.*, not admixed), at different rates of infusion. As such, Applicants submit that the metes and bounds of amended claim 3 are definite and request that this rejection be withdrawn.

35 U.S.C. § 112, first paragraph

Claim 3 is also rejected under 35 U.S.C § 112, first paragraph as lacking enablement. The Examiner contends that while the specification is enabled for the use of an inorganic nitrite with a red cell substitute containing hemoglobin, it is not enabled for the use of erythrocytes and inorganic nitrite.

In the interest of furthering prosecution, without acquiescing to the Examiner's remarks, Applicants have amended claim 3 to delete the recitation of "red blood cells" (*i.e.*, erythrocytes). As such, this rejection has been overcome and should be withdrawn.

Claim Rejection under 35 U.S.C. § 103

Claim 3 is rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 96/30006 ("the 96 publication"). According to the Examiner, the '96 publication teaches the concurrent administration of a hemoglobin-containing blood substitute and sodium nitrite, and also teaches the nitrosylation of proteins *in vivo* as a therapeutic modality for treating or preventing vasoconstriction associated with the infusion of blood substitutes containing hemoglobin.

Amended claim 3 recites a method of blood product transfusion comprising the steps of co-administering a hemoglobin-containing blood substitute and an inorganic nitrite into a patient via infusion, wherein the inorganic nitrite is infused at a rate of 0.01 to 10 micromoles per

minute, and the hemoglobin-containing blood substitute is infused at a rate of 1 to 1000 cubic centimeters per hour. New claims 7-12 depend directly or indirectly from claim 3.

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. *See In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988). It is also well recognized that a prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *See W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). Further, it is improper to combine references where the references teach away from their combination. *See In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

Moreover, the mere fact that these references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one ordinary skill in the art. *See* MPEP §2143.01, citing *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385, 1396 (2007). Furthermore, a statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *See* MPEP §2143.01, citing *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (emphasis original).

Applicants submit there is no objective reason provided by the '96 publication that would provide the skilled artisan with a reasonable expectation that the co-administration of a hemoglobin containing blood substitute with an inorganic nitrite would be effective to decrease morbidity or mortality in patients in need of a blood product transfusion.

Applicants submit that the '96 publication fails to teach that an inorganic nitrite can be used in the disclosed method. Contrary to the Examiner's assertions, inorganic nitrites are not a compounds which directly donate, release or transfer nitric oxide (to be contrasted with organic nitrites) and the discovery here is that inorganic nitrites, under specified conditions, can be converted into species which obviate the adverse effects of hemoglobin/RBCs.

In contrast, the '96 publication teaches that a ***modified*** form of an inorganic nitrite can be used to S-nitrosylate hemoglobin *in vitro*. In particular, the '96 publication teaches S-nitrosylation of hemoglobin *in vitro* using ***acidified*** sodium nitrite. *See* WO96/30006, Example 19 at page 73, lines 14-15. Such acidification, however, destroys hemoglobin. The skilled artisan would readily recognize that inorganic nitrites themselves are incapable of donating, releasing or transferring nitric oxide without acidification. As evidenced by the '96 publication, inorganic nitrites must first be converted into an acidified state in order donate, release or transfer nitric oxide. The skilled artisan would further recognize that acidified sodium nitrite would be toxic upon administration to a human subject, and that the degree of acidification that has been used is not compatible with the biological function of hemoglobin, as evidenced by the '96 publication which only teaches *in vitro* use of acidified sodium nitrite. Thus, the '96 publication *teaches away* from using an inorganic nitrite, such as sodium nitrite, to donate, release or transfer nitric oxide for *in vivo* applications, as required in the claimed invention.

Based on the foregoing, the skilled artisan reading the '96 publication as a whole, as required, would not co-administer a hemoglobin containing blood substitute and an inorganic nitrite intravenously to reach the present invention with predictable results.

Additionally, a determination of whether the claimed subject matter as a whole would have been obvious at the time the invention was made also involves factual findings with respect to secondary considerations, including failure of others and superior/unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

The present invention provides unexpected results which are not taught or suggested by the '96 publication. The Examiner asserts that Example 19 of the '96 publication teaches that equimolar quantities of sodium nitrite and hemoglobin should be reacted and that the quantity of sodium nitrite and the rate of administration can be calculated from the quantity of hemoglobin to be administered. The Examiner further asserts that the claimed concentration range of inorganic nitrite (*i.e.*, infusion of inorganic nitrite at a rate of 0.01 to 10 micromoles per minute) cannot provide patentable subject matter unless there is a surprising result indicating that the concentration is critical.

The claimed infusion rate is in fact essential and critical to the claimed invention. It is well recognized in the art that hemoglobin is easily oxidized by inorganic nitrite resulting into methemoglobin, which can be toxic at elevated levels in the circulation. Co-infusion of an

inorganic nitrite and a blood substitute containing hemoglobin at the claimed infusion rate of 0.01 micromoles to 10 micromoles per minute prevents toxic oxidization of the hemoglobin during infusion. Moreover, the instant invention does not require reacting equimolar quantities of sodium nitrite and hemoglobin (which would not be compatible with life), as taught in the '96 publication. As stated in the specification, the present invention is based upon the discovery that low concentrations of nitrite do not oxidize oxyhemoglobin, as thought, but instead combine with deoxygenated hemoglobin to store NO on heme β -subunit of hemoglobin tetramer to form iron nitrosyl hemoglobin and upon oxygenation the NO is transferred from the heme of β-subunits to thiol of β -cys93 to produce SNO-Hb. *See* specification at page 2, lines 12-16. More specifically, Applicants were the first to discover a method for preparing stable iron nitrosylated hemoglobin readily convertible to SNO-hemoglobin by reacting a low concentration of inorganic nitrite with deoxyhemoglobin (1:10 to 1:1000 mole ratios of nitrite to deoxy-hemoglobin) to form iron nitrosyl hemoglobin, which is a very desirable product because it is stable and generates a hemoglobin product capable of NO delivery (*e.g.*, SNO-Hb) upon oxygenation.

These unexpected and superior properties of the claimed method are not taught or suggested by the '96 publication.

Applicants request reconsideration and withdrawal of the present rejections.

Conclusion

Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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